

PROTOCOL	
Study Title:	A Phase 1/11, 1 :1 Randomized, Multicenter Study for Diabetic Macular Edema Using 0.3mg Ranibizumab Combined with Ultra Wide 200° Field Angiography Guided Pan Retinal Photocoagulation Monthly for 4 Months (Loading Dose), Then as Needed vs. 0.3 mg Ranibizumab 4 Months (Loading Dose) Monotherapy, Then as Needed (DME- <u>AntiVEgf</u>) DAVE
Study drug:	Recombinant Humanized Anti-VEGF Monoclonal Antibody Fragment (rhuFab V2 [ranibizumab])
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1. BACKGROUND

1.1 Disease Overview

Diabetic retinopathy is the leading cause of legal blindness in Americans aged 55-74, accounting for 8% of all legal blindness and 12% of the newly blind (Llein and Klein, 1995). Diabetic retinopathy is a common complication of Type 1 and Type 2 diabetes, as well as for women with gestational diabetes, affecting more than 2.5% of the U.S. population, or more than 5.3 million Americans aged 18 or older (Friedman, et al., 2007).

Age and race appear to play a role in the prevalence of diabetic retinopathy (Friedman, et al., 2007). Caucasians are the most commonly affected in the age group less than 40, as are Hispanics in the older than 40 population. The longer the duration of diabetes, the greater the risk there is of developing diabetic retinopathy.

Three forms of retinopathy are commonly recognized in association with all forms of diabetes mellitus: 1) non-proliferative diabetic retinopathy (NPDR}, 2) proliferative diabetic retinopathy (PDR), and 3) diabetic macular edema (DME).

NPDR is characterized by ophthalmoscopically visible abnormalities that include microaneurysms, intraretinal hemorrhages, exudates, retinal nerve fiber layer infarcts called cotton wool spots, and, in more severe cases, venous beading and intraretinal microvascular abnormalities.

Over time, NPDR may progress to more severe PDR, the hallmark of which is neovascularization on the surface of the retina, optic disc, iris, or anterior chamber angle. PDR is associated with a high risk of visual morbidity arising from vitreous hemorrhage, traction retinal detachment, and neovascular glaucoma (Diabetic Retinopathy Study [DRS] Research Group, 1979).

DME, the third form of diabetic retinopathy, is characterized by swelling of the central part of the retina that mediates high-resolution vision. DME frequently coexists with, and is superimposed upon NPDR or PDR. When the area of swelling

1.2 Treatment of Diabetic Macular Edema

The current standard of care for DME is suboptimal. Although focal laser photocoagulation plays a significant role in the management of patients with DME, its effect is often transient and inadequate. Fewer than 15% of patients gain more than three lines of best-corrected visual acuity (BCVA) at 3 years, whereas > 15% sustain moderate vision loss of more than three lines. Focal laser is less effective in cases of diffuse macular edema. Photocoagulation is a destructive therapy and often causes symptomatic Paracentral scotomas, which can become disabling after multiple treatments. Vitrectomy is often reserved for the most refractory cases of DME and is associated with vitreous traction and bleeding. It also carries surgical risks (cataract formation, retinal detachment, and endophthalmitis) and has not been validated in large, randomized studies.

1.2.1 Glucose Control

Although glucose control does not have a direct treatment effect on macular edema, it plays a role in the management of diabetic retinopathy as a primary and secondary prevention strategy. In the time frame of 3 or more years, improving blood pressure slows progression of retinopathy (DCCT Research Group, 1993; UKPDS Research Group, 1998a, 1998b). The cumulative incidence and progression of retinopathy, defined as a change of three or more steps on fundus photography (FP) sustained over a 6-month period, was similar in the two treatment groups (conventional and intensive glucose control) until approximately 3 years. By 5 years of follow-up, there was a significant reduction in the risk of sustained progression of retinopathy by 78% in the intensive therapy group compared with the conventional therapy group in the primary prevention cohort. In the secondary intervention cohort, the progression of retinopathy was reduced by 54% in the intensive therapy group during the entire study period compared with those assigned to the conventional therapy group, while the need for laser treatment was reduced by 56%. This suggests that glycemic control is not necessarily efficacious in reducing the progression of retinopathy. There was a reduction in the incidence and progression of retinopathy for those receiving intensive treatment earlier in the course

likely to lose 15 or more letters on the ETDRS visual chart at 3 years than those who were not (12% vs. 25%). For the CSME-CI subgroup of CSME, subjects assigned to receive early macular laser photocoagulation were also less likely to lose 15 or more letters at 3 years than those who were not (13% vs. 33%) (ETDRS Research Group 1987). In a more recent study comparing laser photocoagulation with intravitreal corticosteroids for DME involving the fovea, laser-treated patients gained a mean of +1 ETDRS letter from baseline to 2 years, and +5 ETDRS letters from baseline to 3 years. At 2 years, 14% of laser-treated patients had lost 15 or more ETDRS letters, and 18% had gained 15 or more ETDRS letters. Among patients who completed 3 years from study baseline, 30% of patients treated with laser photocoagulation improved by 15 or more ETDRS letters, and 9% lost 15 or more ETDRS letters (Diabetic Retinopathy Clinical Network, 2008 and 2009). Although photocoagulation for CSME-CI is a significant achievement in the management of diabetic retinopathy, laser treatment still leaves 9%-13% of patients losing more than 15 letters of vision at the end of 3 years. Moreover, given that 69% of subjects with CSME in the ETDRS group had center involvement at presentation (ETDRS Research Group 1987), the unmet clinical need for better treatment of CSME-CI is significant.

1.2.3 Intravitreal Corticosteroids

Limited clinical experience from non-randomized case series provided early evidence of therapeutic effect from intravitreal corticosteroids for the management of focal and diffuse DME. The biologic basis for the suggested beneficial effect most likely derives from the ability of corticosteroids to inhibit VEGF gene expression (Nauck et al., 1998). In a study of 26 eyes of 20 subjects by Jonas et al. (2006), a single 25 mg intravitreal injection of triamcinolone acetonide (TA; Kenalog[®]) was associated with a significant mean VA improvement ($p < 0.001$) from 20/165 at baseline to 20/105 at the end of a 6-month follow-up. In comparison, 16 subjects observed in a "control group" that received grid laser photocoagulation showed no improvement in VA. In a separate uncontrolled study of 16 eyes with CSME that did not respond to laser photocoagulation, a 4-mg intravitreal injection of TA resulted in mean VA improvement of 2.4, 2.4, and 1.3 Snellen lines and reduction of central macular thickness by 55%, 57%, and 38% measured at the 1, 3, and 6-month follow-up intervals, respectively (Martidis et al. 2002). In a third study of 12 subjects (24

anatomy. These "pulling" vector forces on the retina may cause and exacerbate macular edema. Cases such as these, in which a mechanical traction complicates the pathology of macular edema, are less responsive to laser therapy, and presumably, intravitreal corticosteroids. Vitrectomy may play a role in this setting to prevent severe vision loss. Some studies of subjects with DME have reported DME resolution in 45%-82% of eyes, and VA improved by two or more lines in 49%-86% of subjects (van Effenterre et al., 1993; Tachi and Ogino 1996; Pendergast et al. 2000).

1.2.5 Pegaptanib Sodium Injection

Results from an experimental anti-VEGF therapy, pegaptanib sodium injection (Macugen®), showed evidence of biologic effect in DME. Pegaptanib is an inhibitory aptamer, currently approved for the treatment of neovascular (wet) age-related macular degeneration (AMD). It is delivered as an intravitreal injection every 6 weeks.

In a Phase II, double-masked, sham-controlled study of 172 subjects with DME, 73% of those receiving 0.3 mg pegaptanib experienced stable or improved vision (defined as < 15-letter loss) at Week 36 compared with 51% of those who received a sham injection ($p = 0.023$) (Cunningham et al. 2005). Among subjects treated with 0.3 mg pegaptanib, 59% reported a vision gain of at least one line (5 letters) versus 34% of those given sham injections ($p = 0.010$); 34% reported a vision gain of at least two lines (10 letters) versus 10% of those given sham injections ($p = 0.003$); and 18% reported vision gain of at least three lines (15 letters) versus 7% of sham ($p = 0.12$). In addition, 42% of subjects receiving 0.3 mg pegaptanib showed a decrease of at least 100 μm in mean retinal thickness compared with 16% of those receiving sham injections. Additionally, at the end of the study, only half as many subjects who received pegaptanib needed additional laser therapy compared with those receiving usual care (25% vs. 48%) (Cunningham et al. 2005). The study adds further evidence that intravitreal anti-VEGF therapy for DME is tolerated and could provide benefit in this disease process.

1.2.6 Bevacizumab

Bevacizumab (marketed under the trade name Avastin®) is an anti-VEGF monoclonal

showed that three monthly injections of 0.3 mg or 0.5 mg ranibizumab were tolerated by subjects with CSME-CI. At 3 months, 4 of 10 subjects gained ;;;: 15 letters, 5 of 10 subjects gained ;;;: 10 letters, and 8 of 10 subjects gained ;;;: 1 letters. At Month 3, the 0.5 mg and 0.3 mg ranibizumab groups demonstrated a change of+ 7.8 (A} 8.1) and+ 12 (A} 20) letters in mean BCVA. The mean decrease in retinal thickness of the center point of the central subfield was 45.3 A} 196.3 μ m for the low-dose group and 197.8 A} 85.9 μ m for the high-dose group. Although subjects in both dose arms showed improved BCVA from baseline to 6 months on average, the anatomic and functional outcomes were better for the high-dose group.

In another Phase I, Genentech-supported 1ST, results are available on 10 subjects with CSME-CI who received the higher dose (0.5 mg) of ranibizumab with three initial monthly injections followed by retreatment every 2 months. Mean BCVA increased significantly to+ 12.3 letters at 7 months, with a corresponding decrease of- 246 μ m in mean foveal thickness. This effect was seen despite prior multiple laser treatments in 8 of the 10 subjects and prior intravitreal triamcinolone treatment in 3 subjects. Similar to data from Genentech's AMO clinical trials of ranibizumab, the onset of effect occurred after the first dose and was sustained with monthly injections. A slight attenuation of anatomic outcome was seen with the 2-month retreatment interval but a return of benefit was evident after re-injection (Nguyen et al. 2006).

1.4 Nonclinical Experience with Ranibizumab

1.4.1 Nonclinical Pharmacokinetics

The pharmacokinetics of ranibizumab have been investigated in rabbits and cynomolgus monkeys following intravitreal and intravenous administration. In both species, following intravitreal administration, ranibizumab was cleared from the vitreous humor with a half-life of 2-3 days. Following single intravitreal administration to cynomolgus monkeys, retinal concentrations of ranibizumab were approximately one third of vitreous concentrations and declined in parallel with vitreous concentrations. In humans, the intravitreal half-life of ranibizumab is estimated to be 7-8 days. Repeated intravitreal injections of ranibizumab can lead to detectable antibodies in serum in rabbits and cynomolgus monkeys.

Although there was a low rate (<4%) of arterial thromboembolic events (ATEs) observed in the ranibizumab clinical trials there is a potential risk of ATEs following intravitreal use of inhibitors of VEGF. The rate of ATEs in three studies (FVF2598g, FVF2587g, and FVF3192g) in the first year was 1.9% of subjects in the combined group of subjects treated with 0.3 mg or 0.5 mg ranibizumab compared with 1.1% of subjects in the control arms of the studies. In the second year of Study FVF2598g and FVF2587g, the rate of ATEs was 2.6% of subjects in the combined group of those treated with 0.3 mg or 0.5 mg ranibizumab compared with 2.9% of subjects in the control arm. The most common non-ocular adverse reactions observed in 15% of ranibizumab-treated subjects that occurred more frequently than in control subjects included, nasopharyngitis, headache, and upper respiratory tract infection.

The Sailor study (FVF3689g) evaluated the safety of intravitreal ranibizumab in a large population of subjects with CNV secondary to AMO. Subjects in Cohort 1 (N=2378) were randomized (1:1) to receive ranibizumab at a dose level of 0.3 mg or 0.5 mg; subjects were masked to these dose levels. Treatment was administered monthly for three initial doses (Day 0, Month 1, and Month 2), with scheduled follow-up visits on Months 3, 6, 9, and 12. Retreatment after the first three injections was performed as needed, on the basis of predefined criteria with injections no more frequently than every 30 days.

Cohort 2 (N=1992) consisted of subjects enrolled after the majority of Cohort 1 subjects had been enrolled, with enrollment continuing until ranibizumab was approved or denied by the FDA for US marketing, and if approved, until commercially available or 30 September 2006, whichever was earlier. Subjects in Cohort 2 received open-label ranibizumab at the 0.5 mg dose level, with an initial injection on Day 0 followed by retreatment at the physician's discretion, no more frequently than every 30 days. Subjects were monitored for safety for a total of 12 months; safety information, including both serious and nonserious adverse events, was collected at every clinic visit, with two formal safety visits scheduled at Months 6 and 12.

field angiography guided pan retinal photocoagulation for the treatment of CSME secondary to diabetes mellitus (Type 1 or Type 2).

2.1 Primary Objectives

The following primary objective measures will be evaluated:

- 1) Assess number of ranibizumab injections in each of the two cohorts required through Month 36.
- 2) Evaluate the mean change over time in ETDRS BCVA through Month 36
- 3) Incidence and severity of ocular and non-ocular adverse events (AE's) through Month 36.

2.2 Secondary Objectives

The following secondary outcome measures will be evaluated:

- 1) Percentage of patients who experience a loss of 15 or more letters from Baseline to Month 12, 24, and 36 in ETDRS BCVA.
- 2) Determine percentage of patients who experience a gain of 15 or more letters from Baseline to Month 12, 24, and 36 in ETDRS BCVA.
- 3) Evaluate mean change in central retinal thickness over time through Month 12, 24, and 36 as assessed by high resolution OCT's.
- 4) Percentage of patients with persistent macular edema post-intravitreal injection.
- 5) Mean change in peripheral visual field as measured by Goldmann visual field at screen and Months 12, 24, and 36.

3. STUDY DESIGN

3.1 Description of the Study

This study is a Phase 1/11, multicenter, randomized, study of the efficacy and safety of 0.3 mg ranibizumab injection monotherapy verses a dual therapy of 0.3 mg ranibizumab combined with ultra wide 200° field angiography guided pan retinal photocoagulation in patients with CSME-CI secondary to diabetes mellitus (Type 1 or 2).

C). After the first session of PRP, subject's will have ultra wide 200° field angiography performed every 3 months to indicate areas of peripheral ischemia, which will be selectively treated at V9 (Month 6), V21 (Month 18), and V28 (Month 25), preserving areas of more perfused retina. This will minimize any visual field loss secondary to nonselective pan-retinal photocoagulation.

3.2 Rationale for Study Design

Ranibizumab is a Fab antibody with a high affinity and specificity for VEGF-A. VEGF-A plays a critical role in DME as a driving factor for retinal vascular permeability, which is the main cause of visual impairment in patients with center-involving CSME. Based on nonclinical data and clinical experience in AMO and DME, the 0.5 mg and 0.3 mg ranibizumab doses were selected to characterize the safety and efficacy of intravitreal ranibizumab injections in subjects with CSME-CI. Both doses have established safety and efficacy profiles in subjects with neovascular AMO. The primary efficacy endpoint, the percentage of subjects gaining ≥ 15 letters at 12 months, was chosen to demonstrate benefit to visual function and has been used as a functional endpoint in prior studies of ranibizumab in AMO.

The RISE/RIDE protocol determined that only 30% of all subjects getting monthly intravitreal injections of 0.5 mg ranibizumab were completely dry on OCT measurement. The rationale of the DAVE study is the addition of ultra wide 200° field angiogram guided pan-retinal photocoagulation will reduce the VEGF drive and increase visual function and decrease the total number of intravitreal injections needed in a 12-month period.

Compared with prior therapies, ranibizumab is highly effective in preventing or reducing vision loss. In the pivotal Phase III clinical studies of ranibizumab for neovascular AMO, MARINA and ANCHOR, approximately 95% of treated patients achieved the primary visual acuity (VA) endpoint of losing ≤ 15 letters in the Early Treatment of Diabetic Retinopathy Study (ETDRS) best corrected VA (BCVA), compared with 53% of sham-injected patients and 66% of patients treated with Visudyne®-photodynamic therapy (PDT). A significant number of patients treated with ranibizumab experienced durable improvement in VA. In

3.3 Outcome measures

3.3.1 Primary Outcome Measures

The primary outcome measures for safety and tolerability are the following:

- 1) Mean change over time in EDTRS BCVA through Month 36
- 2) The comparative difference of total number of intravitreal injections between Cohort 1 versus Cohort 2.
- 3) Incidence and severity of ocular and non-ocular adverse events (AEs) through Month 36

3.3.2 Secondary Outcome Measures

- 1) Percentage of subjects who experience a loss of 15 or more letters from Baseline to Months 12, 24 and 36 in ETDRS BCVA.
- 2) Percentage of subjects who experience a gain of 15 or more letters from Baseline to Months 12, 24 and 36 in ETDRS BCVA.
- 3) Mean change in central retinal thickness over time through Months 12, 24 and 36 as assessed by high resolution OCT.
- 4) Mean change in peripheral visual field as measured by Goldmann Visual Field assessed through Month 36.

3.4 Safety Plan

The safety and tolerability of intravitreal ranibizumab injections have been investigated in previous Phase I, 1/11, 111, and IIIb studies in AMD. Potential safety issues associated with the route of administration or the pharmacology of ranibizumab in the study population include decreased BCVA, intraocular inflammation intraocular infection, transient and/or sustained elevation of intraocular pressure (IOP), cataract development or progression, retinal or intravitreal hemorrhage, macular edema, retinal break or detachment, and arterial thromboembolic events (ATEs). Safety will be assessed by visual acuity, ophthalmic examinations including intraocular measurements, fluorescein angiograms, adverse events and vital signs.

To minimize the risks of intraocular injections, all injections will be performed employing

- BCVA score in the study eye of 20/32 to 20/320 approximate snellen equivalent using the ETDRS protocol at an initial testing distance of 4 meters, confirmed by the investigator.
- High Definition OCT (Spectralis) central retinal thickness measurement of $\leq 300\mu\text{m}$
- Decrease in visual acuity is determined to be primarily the result of DME and not to other cause.
- Ability and willingness to return for all scheduled visits and assessments.
- Clear ocular media and adequate pupillary dilatation to permit good quality fundus photography.

4.1.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

General Exclusion Criteria

- Pregnancy (positive pregnancy test) or lactation
- Sexually active women of childbearing potential* who are unwilling to practice adequate contraception or abstinence during the study. (*Although no birth control method is 100% effective, the following are considered adequate means of contraception: surgical sterilization, use of oral contraceptives, barrier contraception using either a condom or diaphragm with spermicidal gel, intrauterine devices, or contraceptive hormone implants or patches. A subject's primary care physician, obstetrician, or gynecologist should be consulted regarding an appropriate form of birth control)
- Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated
- Participation in another simultaneous medical investigation or trial.

Ocular Exclusion Criteria

- Prior Ocular Treatment:
 - o History of vitrectomy surgery in the study eye
 - o Any pan-retinal photocoagulation in the study eye
 - o Prior treatment with intraocular or subconjunctival steroids in the study eye 4 months prior to screen

- Concurrent Systemic Conditions
 - o Uncontrolled blood pressure (defined as systolic > 180 mmHg and/or diastolic > 110 mmHg while patient is seated. *If a subject's initial reading exceeds these values, a second reading may be taken 30 or more minutes later. If the subject's blood pressure needs to be controlled by antihypertensive medication, the subject can become eligible if medication is taken continuously for at least 30 days prior to Day 0
 - o Atrial fibrillation not managed by subject's primary care physician or cardiologist within 3 months of screening visit
 - o History of stroke within the last 3 months of screening visit
 - o History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect the interpretation of the results of the study or renders the patient at high risk for treatment complications
 - o Current treatment for active systemic infection
 - o Active malignancy
 - o History of allergy to fluorescein, not amenable to treatment
 - o Inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analyzed and graded.
 - o Previous participation in any studies of investigational drugs within 1 month preceding Day 0 (excluding vitamins and minerals)

4.2 Method of Treatment Assignment

Cohort 1: Subjects will receive 4 mandatory intravitreal injections of 0.3 mg ranibizumab every 28 days(+/- 7 days). They will then be seen monthly(+/- 7 days) and will receive intravitreal injections of 0.3 mg ranibizumab on a PRN schedule per retreatment criteria based on the evaluating Investigator's assessment of disease activity.

Cohort 2: Subjects will receive 4 mandatory intravitreal injections of 0.3 mg ranibizumab every 28 days(+/- 7 days). They will then be seen monthly(+/- 7 days) and will receive intravitreal injections of 0.3 mg ranibizumab on a PRN schedule per

Following the intravitreal injection, subjects will be examined by indirect ophthalmoscopy to make sure there is good perfusion of retinal vessels. Subjects should be instructed to report any symptoms suggestive of endophthalmitis without delay.

c) Storage

Upon receipt, study drug kits should be refrigerated at 2°C - 8°C (36°F - 46°F). DO NOT FREEZE. Do not use beyond the expiration date. Ranibizumab vials should remain refrigerated. Protect vials from direct light. Store in original carton until time of use.

RANIBIZUMAB VIALS ARE FOR SINGLE USE ONLY. Vials used for one subject may not be used for any other subject.

4.4 Concomitant and Excluded Therapies

Subjects may continue to receive all medications and standard treatments administered for their conditions at the discretion of their treating physician.

4.5 Study Assessments

4.5.1 Assessments During the Treatment Period

*Refer to Appendix A for a complete overview of study procedures.

Vital Signs

Vital signs will include measurements of pulse and systolic and diastolic blood pressure while the patient is in a seated position. Vital signs should be taken before injection of ranibizumab.

Ocular Assessments

- BCVA at a starting distance of 4 meters at all visits
- IOP measurement (perform prior to dilating eyes; the method used for a subject must remain consistent throughout the study)
- Slit lamp examination
- Dilated binocular indirect high-magnification ophthalmoscopy
- Goldmann Visual Field, study eye only
- Anterior chamber paracentesis (aqueous)

- 5) Pegaptanib sodium injection treatment in either eye
- 6) SAE
- 7) Any other safety concerns
- 8) In the event of an adverse event in the study eye that is considered by the Investigator to be severe in intensity, serious consideration should be given to discontinuing the subject from the study.

4.7 Study Discontinuation

Retina Consultants of Houston or Genentech may terminate this study at any time.

Reasons for terminating the study may include the following:

- 1) The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- 2) Subject enrollment is unsatisfactory
- 3) Data recording is inaccurate or incomplete

4.8 Statistical Methods

4.8.1 Analysis of the Conduct of the Study

The analysis of data from the 36-month treatment period will be performed when all patients have either completed the visit at Month 36 or discontinued early from the study. Treatment assignment will be unmasked to the personnel performing the analysis when all data collected through Month 36 are in the database and the data have been cleaned and verified.

The analysis of complete data (36-month treatment period) for the study will be performed when all patients have either completed the visit at Month 36 or discontinued early from the study, all data collected from the study are in the database, and the database is locked. Aggregate results of the 36-month analysis, summarized by treatment group, may be reported to the public before completion of the study.

This is a phase 1/2 study with 40 subjects, descriptive summaries will be provided for the specified co-primary endpoints, comparisons will be performed for hypothesis generating purposes only and no definitive inference will be made. Thus, multiplicity adjustments are not planned.

A. Primary Endpoints

- 1) Mean change in number of intravitreal injections through Month 36.
- 2) Mean change over time in ETDRS BCVA from Baseline through Month 36.
- 3) Incidence and severity of ocular and non-ocular adverse events (AEs) through Month 36.

B. Secondary Endpoints

- 1) Percentage of subjects who experience a loss of 15 or more letters from Baseline to Month 12, 24, and 36 in ETDRS BCVA.
- 2) Percentage of subjects who experience a gain of 15 or more letters from Baseline to Month 12, 24, and 36 in ETDRS BCVA.
- 3) Mean change in central retinal thickness over time through Month 12, 24, and 36 as assessed by high resolution OCT.
- 4) Mean change in peripheral visual acuity as measured by Goldmann Visual Field assessed through Month 36.

4.8.6 Missing Data

Analyses of efficacy and safety will be based on available cases, without imputation for missing values.

4.8.7 Interim Analyses

No formal schedule of interim analyses is planned. Reports of adverse events from the study may be reviewed and summarized periodically while the study is ongoing to ensure the safety of subjects.

4.9 Data Quality Assurance

- 3) It requires or prolongs inpatient hospitalization.
- 4) It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- 5) It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- 6) It is considered a significant medical event by the Investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

5.3 Methods and Timing for Assessing and Recording Safety Events

The Investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product by either Genentech, Inc. or a Regulatory Authority, including:

- Lack of Effect
- Endophthalmitis
- Intraocular Inflammation (including vitritis and uveitis)
- Cataract (traumatic)
- Increased IOP
- ATE's including stroke
- Retinal Pigment Tear
- Retinal Detachment

Reconciliation of Single Case Reports

The Parties will ensure that Genentech, Inc., has adequately received all Single Case Reports via the exchange of a line listing documenting Single Case Reports sent by site in the preceding time period (e.g. monthly). Confirmation of receipt should be received within the time period mutually agreed upon.

Unexpected adverse events are those not listed in the Package Insert (P.1.) or current Investigator Brochure (1.8.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or 1.8. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or 1.8. only referred to elevated hepatic enzymes or hepatitis.

5.4 Evaluations

Ophthalmologic evaluations will include slit lamp examination, dilated binocular indirect high magnification ophthalmoscopy, measurements of BCVA and intraocular pressure, and indirect ophthalmoscopy. (See Section 4.5 for a detailed description of the study assessments).

5.5 Vital Signs

Pulse and blood pressure will be measured at protocol specified study visits (See Section 4.5).

5.6 Procedures for Eliciting, Recording, and Reporting Adverse Events

5.6.1 Eliciting Adverse Events

A consistent methodology for eliciting AE's at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

5.6.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a) Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs

- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

e) Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the {study drug} should be reported as an SAE.

f) Post-Study Adverse Events

The Investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior {study drug} exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g) SAE Reporting

Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682

OR

(650) 225-5288

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available
- Serious AE reports that are related to the ranibizumab will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the ranibizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

- For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study.
- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at:

<http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>

5.6.5 Additional Reporting Requirements for IND Holders

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in CFR § 600.80

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

- The Investigator is required to notify the FDA of and fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of ranibizumab. An unexpected adverse event is one that is not already described in the ranibizumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.
- The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report (see Appendix D), of any serious, unexpected AE that is considered reasonably or possibly related to the use of ranibizumab. An unexpected adverse event is one that is not already described in the ranibizumab Investigator Brochure.
 - Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Genentech Supported Research

AE/SAE Fax Number(s): (650) 225-4682 OR (650) 225-5288

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone#	
Reporter Fax#	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	 []-[]-[]
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SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

6. INVESTIGATOR REQUIREMENTS

6.1 Study Initiation

Before the start of this study, the following documents must be on file with Retina Consultants of Houston or its appointed representative:

- FDA correspondence letter assigning an IND number or an IND waiver letter

The informed consent document must be signed and dated by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The following basic elements must be included:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures or drug used for purposes which are experimental
- A description of any reasonable foreseeable risks or discomforts to the subjects
- A description of any benefits to the subjects or to others, which may reasonably be expected from the research
- A description that there may be no benefit from this research
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
- A statement describing the extent, if any, to which confidential records identifying the subject will be maintained and that notes the possibility that the FDA and Retina Consultants of Houston and the drug manufacturer may inspect the records
- For research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatments are available should injury occur and, if so, what they consist of or where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject

change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID ON THE ORIGINAL.

6.6 Study Drug Accountability

The Investigator is responsible for the control and distribution of study drug.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedures.

6.7 Disclosure of Data

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

With the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, the drug manufacturer and the IRB/EC for each study site, if applicable.

6.8 Retention of Records

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the investigation is discontinued and the U.S. FDA and the applicable national local health authorities are notified.

6.9 Study Close-out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to

7 . REFERENCES

1. Chun DW, Heier JS, Topping TM, Duker JS, Bankert JM. A pilot study of multiple intravitreal injections of ranibizumab in patients with center-involving clinically significant diabetic macular edema. *Ophthalmology* 2006;113:1706-12.
2. Cohen T, Nahari D, Cerem LW, Neufeld G, Levi BZ. Interleukin 6 induces the expression of vascular endothelial growth factor. *J Biol Chem* 1996;271:736-41.
3. Cunningham ET Jr, Adamis AP, Altaweel M, Aiello LP, Bresler NM, D'Amico DJ, et al. on behalf of the Macugen Diabetic Retinopathy Study Group. A Phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. *Ophthalmology* 2005;112:1747-57.
4. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
5. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetate and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2008;115:1447-9, 1449.e1-10.
6. Diabetic Retinopathy Clinical Research Network (DRCR.net), Beck RW, Edwards AR, Aiello LP, et al. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Arch Ophthalmol* 2009;127:245-51.
7. *Diabetic Retinopathy Clinical Research Network Writing Committee. Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010 (In-Press).*
8. Diabetic Retinopathy Study Research Group. Four risk factors for severe visual loss in diabetic retinopathy. *Arch Ophthalmol* 1979;97:654-5.
9. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. ETDRS Study Report Number 1. *Arch Ophthalmol* 1985;103:1796-806.
10. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. ETDRS Report

- results of a prospective controlled trial. *Ophthalmology* 2004;111:218-24.
22. Nauck M, Karakiulakis G, Perruchoud AP, Papakonstantinou E, Roth M. Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. *Eur J Pharmacol* 1998;341:309-15.
 23. Nguyen QD, Tatlipinar S, Shah SM, Haller JA, Quinlan E, Sung J, et al. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. *Am J Ophthalmol* 2006;142:961-9.
 24. Pendergast SD, Hassan TS, Williams GA, Cox MS, Margherio RR, Ferrone PJ, et al. Vitrectomy for diffuse diabetic macular edema associated with a taut premacular posterior hyaloids. *Am J Ophthalmol* 2000;130:178-86.
 25. Tachi **N**, Ogino **N**. Vitrectomy for diffuse macular edema in cases of diabetic retinopathy. *Am J Ophthalmol* 1996;122:258-60.
 26. U.K. Prospective Diabetes Study Research Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998a;352:837-53.
 27. U.K. Prospective Diabetes Study Research Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J* 1998b;317:703-13.
 28. van Effenterre G, Guyot-Argenton C, Guiberteau B, Hany I, Lacotte JL. Macular edema caused by contraction of the posterior hyaloids in diabetic retinopathy: surgical treatment of a series of 22 cases. *J Fr Ophtalmol* 1993;16:602-10.
 29. Vinorez SA, Derevjani **NL**, Ozaki H, Okamoto **N**, Campochiaro PA. Cellular mechanisms of blood-retinal barrier dysfunction in macular edema. *Doc Ophthalmol* 1999;97:217-28.
 30. Witmer AN, Vrensen GF, Van Noorden CJ, Schlingemann RO. Vascular endothelial growth factors and angiogenesis in eye disease. *Prag Retin Eye Res* 2003;22:1-29.

Schedule of Events

		Month 19			Month 20			Month 21			Month 22		
		Visit 22			Visit 23			Visit24			Visit 25		

Appendix B

Pre-administration, Administration, and Post-administration Procedures for Intravitreal Injections

The following procedures will be implemented to minimize the risk of potential adverse events associated with intravitreal injections (e.g., endophthalmitis). Staff will observe aseptic technique involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration. In addition to the procedures outlined below, added safety measures in adherence to specific institutional policies associated with intravitreal injections will be observed.

The technician assembles the supplies and prepares a sterile field. Supplies include 10% povidone iodine swabs, sterile surgical gloves, 4x4 sterile pads, pack of sterile cotton-tipped applicators, eyelid speculum, sterile ophthalmic drape, 0.5% proparacaine hydrochloride, 5% povidone iodine ophthalmic solution, 1% lidocaine for subconjunctival injection, ophthalmic antimicrobial solution (e.g., trimethoprim-polymyxin B ophthalmic solution, ofloxacin ophthalmic solution, ophthalmic gatifloxacin solution, ophthalmic moxifloxacin solution), and injection supplies.

Pre-Administration

- Instill topical anesthetic.
- Instill an ophthalmic antibiotic.
- Subconjunctival anesthesia is optional per investigator's discretion: injection 0.5 ml of 2% lidocaine without epinephrine at the injection site.
- Disinfect the periocular skin and eyelid of the study eye. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Make certain that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects. At investigator's discretion, different antiseptic may be used for periocular preparation.

Appendix C

Pan-Retinal Photocoagulation (PRP)

Pan-Retinal Photocoagulation can be performed with topical anesthesia, subconjunctival anesthesia or retrobulbar anesthesia with local anesthetic as detailed below:

Topical Anesthesia

- Apply topical anesthetic onto the study eye
- Wait 3-5 minutes and apply additional topical anesthetic onto the study eye
- Allow 3-5 minutes for anesthesia to be fully effective before administering laser

Subconjunctival Anesthesia

- Apply topical anesthetic onto the study eye
- In a disposable, sterile, 1cc syringe, draw up 0.5cc of 2% injectable lidocaine without epinephrine with a 27g, ½" needle
- Replace the 27g needle with a 30g, ½" needle
- The treating physician should administer the lidocaine subconjunctivally in the study eye
- Allow 3-5 minutes for anesthesia to be fully effective before administering laser

Retrobulbar Anesthesia

- Place the subject in a supine position
- Prepare the study eye for local anesthesia by cleaning the injection area directly below the lower lid of the study eye with an alcohol prep pad
- Apply topical anesthetic onto the study eye
- In a disposable, sterile, 5cc syringe draw up 5cc of 2% injectable lidocaine without epinephrine with a 22g, 1 ½" needle
- Replace the 22g needle with a 25g, 1 ½" needle
- The treating physician should insert the needle into the retrobulbar space and inject the lidocaine. After withdrawing the needle, apply firm pressure to the injection site and the eye for approximately 2 minutes.

Appendix D

Template for IND Safety Reports including Analysis of Similarities

Case Summary

This section will be initiated by a research coordinator and may be modified by Principal Investigators, if necessary. The case summary should describe the reported AE in detail, including a description of what happened and a summary of all relevant clinical information (e.g. medical status prior to the event, signs, symptoms, diagnoses, clinical course, treatment, outcome, etc.) The IND safety report should not identify the subject ID #, reporting Investigator, or the site as this information may compromise the study blind.

Previous Reports

The information for this section comes from Principal Investigator and the search of similar events. This section should be written by the responsible Principal Investigator.

Select one of the following two statements after reviewing the search of similar events results:

- Under IND _____ (insert IND#), the following IND Safety Reports of similar AE's have been previously submitted:

MCN	<u>Reported</u> Event	Submission Date

OR

- Under IND _ _ _ _ _ (insert IND#), no IND Safety Reports of similar AEs have been submitted previously.

In addition to previously submitted IND Safety Reports of similar events, this section can also summarize previous serious reports of the same/similar event that were considered unrelated to the investigational product at the time of the reporting. These events would

- After review of the clinical details and Investigator's comments pertaining to this AE, and based on experience to date, Retina Consultants of Houston does not believe that changes to the conduct of this clinical trial are warranted.
(This statement can be modified if changes to the conduct of the clinical trial are made).